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ISSUE HIGHLIGHTS

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Happy Valentine's Day!

Clinical Practice Guidelines and Patient Care

Clinical practice guidelines or treatment guidelines are being developed throughout the health care industry as a means to reduce inappropriate care, and thereby improve patient care. Attitudes about practice guidelines vary among clinicians, administrators, and patients; however, the goal of all parties is to improve the quality of patient care.[1-4] Improvement in patient care occurs in several steps (Table 1). Although improved health outcomes are the best measure of success, intermediate outcomes (e.g., reducing practice variations, changing prescriber practices) may be acceptable. Unfortunately, only limited evidence is available that practice guidelines can achieve any of these outcomes.[1,4]

A recent study examined the effectiveness of clinical guidelines in improving the process and outcome of patient care. A literature search identified 59 studies (24 on specific clinical conditions, 27 on preventive care, and 8 on prescribing or support services) that evaluated guidelines in terms of the process of medical care or patient outcome. In all but 4 of the 59 studies, a significant change was detected in the process of care in the direction proposed by the guidelines; however, the size of improvement varied across the studies. Nine of the 11 studies that assessed patient outcome reported some significant improvement. Based on this information, guidelines developed through rigorous research design can improve clinical practice.[4]

The potential benefits of clinical guidelines must be balanced against the potential adverse effects of practice guidelines. Many clinicians view guidelines as a threat to their autonomy. Additionally, there is concern that "cookbook medicine" may promote an unhealthy uniformity in medicine that does not respect patient or practice differences and may discourage young clinicians from acquiring clinical reasoning skills.[1,2]

Guidelines are intended to be educational and offer guidance to the prescriber to help them decide how to best care for patients. However, simply distributing practice guidelines to prescribers does not change behavior. The successful introduction of clinical guidelines depends on many factors, including the clinical context and the methods for developing, disseminating, and implementing those guidelines[4] (Table 2). Some groups in the private sector favor enforcement programs to ensure

compliance with guidelines. These programs may include precertification for procedures and medical review and licensing or specialty recertification barriers if guidelines are not followed.[1]

These enforcement programs would not be a problem if there were complete certainty that the guidelines promised optimal care for all patients. Unfortunately, science cannot define optimal care with certainty. Typical studies often leave questions about the generalizability of the results to patients outside the study setting.[1] This is often the case when using efficacy data from controlled, clinical trials as a surrogate for effectiveness data in pharmacoeconomic analyses. Additionally, the process of analyzing evidence and opinion is not perfect. Methods for synthesizing data and gathering expert opinion attempt to maximize objectivity, but this does not guarantee that the guidelines define optimal care.[1] Finally, patients are not uniform. What is best for patients as a whole, may not be best for a particular individual. The patient's medical history and comorbid illnesses may make the guideline's recommended therapy inappropriate for that patient. Patients respond differently to the same treatments, thus standardized approaches often need to be tailored to achieve the best outcomes.[1]

The Pharmacoeconomic Center (PEC) recognizes these limitations in defining optimal care with guidelines. The PEC has published guidelines for the treatment of hypertension, acid-peptic disorders, major depression, and acute respiratory tract infections. Individual MTFs are encouraged to review the PEC's guidelines and adapt them to meet the needs of their prescribers and patients. The PEC provides these treatment guidelines based on the pharmacoeconomic analyses of defined disease states, thus in addition to including efficacy and safety data, these analyses incorporate cost factors that may have been excluded from other published guidelines.

Table 1. Potential Benefits of Practice Guidelines[1]

Step Category	Benefits/Outcomes
Knowledge	Enhanced medical education (medical school, residency, continuing medical education); illustration of how to perform clinical appraisal of evidence; definition of research agenda for future effectiveness studies.
Attitudes	Acceptance of new "standard of care"; enhanced credibility of technologies, specialty
Behavior	Increased compliance with recommended practices; decreased practice variations
Outcomes	Improved clinical outcomes (e.g., morbidity, mortality); decreased costs; enhanced value of health care

Table 2. Strategies for Guideline Introduction[4]

Probability of Being Effective	Development Strategy	Dissemination Strategy	Implementation Strategy
High	Internal	Specific educational intervention	Patient-specific reminder at time of consultation
Above Average	Intermediate	Continuing education	Patient-specific feedback
Below Average	External, local	Mailing targeted groups	General feedback
Low	External, national	Publication in journal	General reminder

References:
1. Woolf SH. *Arch Intern Med* 1993;153:2646-55.
2. Tunis SR, et al. *Ann Intern Med* 1994;120:956-63.
3. Dans PE. *Ann Intern Med* 1994;120:966-8.
4. Grimshaw JM, Russell IT. *Lancet* 1993;342:1317-22.

Pharmacoeconomic Center Q & A.....

Question: When will the Tri-Service Formulary (TSF) be completed? When will the drug reviews be finished?

Answer: The TSF, like any formulary, is continually changing to meet our patients needs, and thus, is never "complete". As new medical information concerning new or existing products becomes available, it must be evaluated and

incorporated into any formulary decisions.

The PEC has completed disease state reviews for hypertension, acid-peptic diseases, major depression, and acute respiratory tract infections. These disease states will be re-evaluated approximately 2 years after the analyses and guidelines have been disseminated to MTFs. This time frame allows adequate time for MTF implementation of the disease state guidelines. This time frame also allows MTFs to collect drug use information for the PEC to incorporate into future analyses.

The PEC plans to continue evaluating the disease states that drive pharmaceutical expenditures. Currently, the focus is in the ambulatory care setting. In the future, this focus will be expanded to include inpatient care as well.

Question: Why were no 2nd or 3rd-tier antibiotics chosen for the Tri-Service Formulary for the treatment of acute respiratory tract infections?

Answer: The PEC evaluated the outpatient treatment of acute respiratory tract infections, including community-acquired pneumonia, bronchitis, sinusitis, and otitis media in a pharmacoeconomic analysis. Because the PEC limited the evaluation to these specific illnesses, only antibiotics commonly used to treat these infections were included in the analysis. This analysis was not intended to be a comprehensive review of antibiotic therapy.

Although acute respiratory tract infection encompasses a variety of clinical diagnoses, three basic premises guide therapeutic decisions for these infections: (1) these illnesses are usually episodic and transient in nature; (2) these illnesses are usually self-limiting in nature; and (3) these illnesses are treated empirically.

The PEC developed a pharmacoeconomic model that included costs associated with physician visits, drug acquisition, and treatment of adverse effects, and included efficacy, adverse effect, and compliance probabilities. The PEC found that treatment costs increased incrementally as drug acquisition costs increased, and differences in clinical efficacy of the drugs were insufficient to overcome this trend. Additionally, costs associated with treatment of severe adverse effects did not affect this trend. In general, the predominant cost associated with an acute respiratory tract infection is the cost of the provider visit.

Based on this information, from a pharmacoeconomic viewpoint, it makes little difference if the first-tier antibiotics are used once a provider visit has occurred. *As drug acquisition price increases with the second and third tier antibiotics, the overall cost of treatment of these infections increases with no corresponding increase in effectiveness of the therapy.* Thus, second and third tier antibiotics should only be used in the event of treatment failure or allergies to all relevant first tier antibiotics.

We would refer you to the discussion by Marchant et al[2] of the "Pollyanna phenomenon" in the treatment of these acute respiratory tract infections.

References: 1. PEC Update 95-03; December 15, 1994.
2. Marchant CD, et al. J Pediatr 1992;120:72-7.

IN CURRENT LITERATURE.....

Cost Analysis of 3-Day Antibiotic Therapy for Acute Cystitis in Women

PEC Update 95-04 described the Mayo Clinic's approach to treatment of uncomplicated cystitis using 3-day antibiotic therapy. A recent study[1] was conducted to determine the efficacy, safety, and costs associated with four different 3-day regimens for the treatment of acute uncomplicated cystitis in women.

Escherichia coli was the only pathogen or copathogen in 85% of patients. The cure rates for each of the four treatment regimens 4 to 6 weeks after treatment are listed in the Table below.

Treatment Regimen	No. Cured/Total Patients (%)
Trimethoprim-Sulfamethoxazole (TMP-SMZ) 160 mg/ 800 mg BID x 3 days	32/39 (82%)
Nitrofurantoin 100 mg QID x 3 days	22/36 (61%)
Cefadroxil 500 mg BID x 3 days	21/32 (66%)
Amoxicillin 500 mg TID x 3 days	28/42 (67%)

Compared with the other treatment regimens, TMP-SMZ was more successful in reducing rectal colonization with E coli soon after therapy and urethral

and vaginal colonization at all follow-up visits. Adverse effects were reported by 25 to 43% of patients.

The mean costs per patient were less with TMP-SMZ ($114) and amoxicillin ($131) compared with nitrofurantoin ($155) and cefadroxil ($155). The higher costs associated with nitrofurantoin and cefadroxil were due to more frequent return visits for treatment of recurrent UTI and/or yeast vaginitis.

The authors did not include a fluoroquinolone regimen in this study because these agents are generally not considered first-line therapy for cystitis mainly because of concerns about emerging resistance to this class of agents. However, based on data from a previous study conducted by the authors,[2] the cost per patient for ofloxacin 200 mg QD for 3 days was similar to that of TMP-SMZ ($115 vs. $114, respectively). Even with this additional information, the authors conclude that TMP-SMZ should be considered the first-line agent for uncomplicated cystitis in women.

This study used the institution's cost for clinic visits and laboratory testing, and average wholesale price plus a pharmacy fee for the drug cost. The use of government prices for visits, laboratory testing, and drugs may change the cost analysis.

References:
1. Hooten TM, et al. JAMA 1995;273:41-5.
2. Hooten TM, et al. Antimicrob Agents Chemother 1991;35:1479-83.

New Drug Approvals - 1994

The Food and Drug Administration approved 22 new molecular entities during 1994. Of these approvals, 12 drugs were designated 1P drugs or new molecular entities that represent a therapeutic gain and represent an advance over current agents. These agents received a priority review. The remaining 10 drugs were classified as 1S drugs and received a standard review. The following table outlines the new drug approvals for 1994.

Generic Name (Brand Name - Sponsor)	Indication/Use	Approval Date
1P Drugs (Priority Review)		
Cysteamine bitartrate (Cystagon - Mylan)	Management of nephropathic cystinosis.	8/15/94
Dorzolamide HCl (Trusopt - Merck)	Treatment of elevated intraocular pressure.	12/9/94
Fludeoxyglucose F18 (none - Downstate Clinical PET Center)	Identification of abnormal glucose metabolism associated with foci of epileptic seizures.	8/19/94
Imiglucerase (Cerezyme - Genzyme)*†	Enzyme replacement therapy for Type I Gaucher's disease	5/23/94
Indium-111 pentetreotide (OctreoScan - Mallinckrodt Medical)	Scintigraphic localization of neuroendocrine tumors with somatostatin receptors.	6/2/94
Iobenguane sulfate I 131 (none - CIS-US)	Adjunctive diagnostic agent in localization of pheochromocytomas and neuroblastomas.	3/25/94
Metformin (Glucophage - Lipha)	Adjunct to diet or sulfonylurea to lower blood glucose in Type II diabetics.	12/29/94
Rimexolone (Vexol - Alcon Labs)	Treatment of postoperative inflammation and anterior uveitis.	12/30/94
Salmeterol xinafoate (Serevent - Glaxo)	Maintenance treatment of asthma and prevention of bronchospasm	2/4/94
Stavudine (Zerit - Bristol-Myers Squibb)†‡	Treatment of adults with advanced HIV who are intolerant of, have significant deterioration on, or have contraindications to other approved therapies.	6/24/94
Tacrolimus (Prograf - Fujisawa USA)†	Prophylaxis of organ rejection in patients receiving allogenic liver transplants.	4/8/94
1S Drugs (Standard Review)		
Acrivastine/Pseudoephedrine HCl (Semprex-D - Burroughs Wellcome)§	Relief of seasonal allergic rhinitis symptoms.	3/25/94
Budesonide (Rhinocort - Astra USA)	Management of symptoms of seasonal or perennial allergic rhinitis in adults and children, and nonallergic perennial rhinitis in adults.	2/14/94
Dalteparin sodium (Fragmin - Pharmacia)	Prevention of deep vein thrombosis in abdominal surgery.	12/22/94
Famciclovir (Famvir - SmithKline Beecham)	Management of acute herpes zoster.	6/29/94
Fluvoxamine maleate (Luvox - Solvay)	Treatment of obsessive-compulsive disorder.	12/5/94
Lamotrigine (Lamictal - Burroughs Wellcome)	Adjunctive therapy of partial seizures in adults with epilepsy.	12/27/94
Nefazodone HCl (Serzone - Bristol-Myers Squibb)	Treatment of depression.	12/22/94
Rocuronium bromide (Zemuron - Organon)	Adjunct to general anesthesia to facilitate tracheal intubation and for skeletal muscle relaxation during surgery or mechanical ventilation.	3/17/94
Spirapril (Renormax - Sandoz)	Treatment of hypertension.	12/29/94
Technetium 99m bicisate (Neurolite - Dupont Merck)	Use in single photon emission CT as adjunct to conventional CT or MRI in localization of stroke.	11/23/94

* orphan drug; † expedited review; ‡ high priority drug for AIDS, accelerated approval; § Semprex-D was designated a "1,4S" drug, indicating a new combination; acrivastine is a new molecular entity. Adapted from: *F-D-C Reports 1995;57(2):8-9.*